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# Strained Enamines as Versatile Intermediates for Stereocontrolled Construction of Nitrogen Heterocycles

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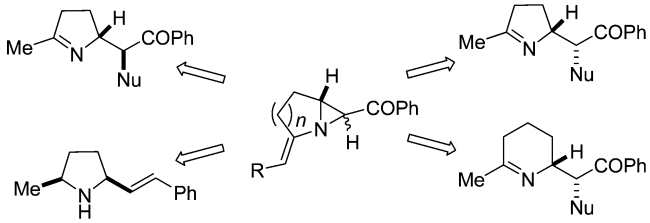


This contribution assesses the synthetic utility of molecules that impose conformational constrains onto aziridine-derived enamines. Synthetically versatile [3.1.0] and [4.1.0] bicyclic enamines have been prepared by intramolecular oxidative cycloamination of aziridine-containing olefins. This process is initiated by *N*-bromosuccinimide followed by base-mediated elimination of HBr to afford highly strained exo-bicyclic enamines. In addition, intramolecular aziridine addition to aldehyde functionality was found to afford the [3.1.0] and [4.1.0] bicyclic hemiaminals. These routes highlight possibilities for chemoselective oxidative transformations of aziridine-containing precursors without nitrogen protection/deprotection steps. The resulting products provide straightforward synthetic entries into a wide range of pyrrolidine- and piperidine-containing heterocycles that are positioned toward subsequent transformations via aziridine ring opening.

## Introduction

The aziridine ring is recognized as a valuable building block for construction of nitrogen-containing molecules.[1] For example, aziridinecarboxylates have been used as intermediates in the synthesis of amino acids.[2] Cycloadditions of *N*-protected aziridines with Pd−trimethylenemethane complexes afford protected piperidines.[3] Under Lewis acid activation, *p*-toluenesulfonyl-containing aziridines undergo cyclization with $\pi$-nucleophiles to afford six-membered heterocycles.[4] 2-Methyleneaziridine phenylselenide derivatives undergo radical cyclizations to produce functionalized piperidines or bicyclic octahydroindolizines.[5] In the large-scale synthesis of Sch 39166, a dopamine $D_1$ receptor antagonist, methylated aziridinium salt was used as the key intermediate, which was later reacted with Grignard reagents.[6] Despite these advances, aziridines are still underutilized in complex molecule synthesis.[7] If functionalization of an aziridine-containing building block is required during synthesis, nitrogen protection/deprotection sequences typically present challenges due to susceptibility of aziridines to premature ring opening.

Our interest in synthetic applications of functionalized aziridines[8] has led us to evaluate the utility of aziridine-containing strained enamines in the synthesis of larger nitrogen-containing heterocycles. We became interested in examining the extent of interaction between aziridine nitrogen and enamine double bond and pursued applications of aziridine enamines as synthetic

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(1) Yudin, A. K., Ed. *Aziridines and Epoxides in Organic Synthesis*; John Wiley & Sons: New York, 2006.

(2) For review, see: Lee, W. K.; Ha, H. *Aldrichimica Acta*. **2003**, *36* (2), 57−63.

(3) Hedley, S. J.; Morgan, W. J.; Prenzel, A. H. G. P.; Price, D. A.; Harrity, J. P. A. *Synlett.* **2001**, 1596−1598.

(4) Bergmeier, S. C.; Katz, S. J.; Huang, J.; McPherson, H.; Donoghue, P. J.; Reed, D. D. *Tetrahedron Lett.* **2004**, *45*, 5011−5014.

(5) (a) Prevost, N.; Shipman, M. *Org. Lett.* **2001**, *3*, 2386-2385. (b) Prevost, N.; Shipman, M. *Tetrahedron* **2002**, *58*, 7165−7175.

(6) Draper, R. W.; Hou, D.; Iyer, R.; Lee, G. M.; Liang, J. T.; Mas, J. L.; Tormos, W.; Vater, E. *J. Org. Proc. Res. Dev.* **1998**, *2*, 175−185.

(7) For use of aziridines in complex molecule synthesis, see: Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599−619.

(8) (a) Siu, T.; Yudin, A. K. *J. Am. Chem. Soc.* **2002**, *124*, 530−531. (b) Caiazzo, A.; Dalili, S.; Yudin, A. K. *Org. Lett.* **2002**, *4*, 2597−2560. (c) Sasaki, M.; Dalili, S.; Yudin, A. K. *J. Org. Chem.* **2003**, *68*, 2045−2407. (d) Watson, I. D. G.; Yudin, A. K. *Curr. Opin. Drug Discovery. Dev.* **2002**, *5*, 906−917.

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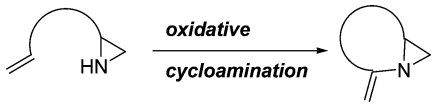
**SCHEME 1**




intermediates. Enamines are among the most widely used building blocks in synthesis. A conventional enamine acts as a nucleophile in a chemical transformation by enlisting its nitrogen lone pair toward nucleophilic attack. However, the aziridine enamine has no such option due to a high kinetic barrier, leading to the strained iminium species.[9] During our initial foray into this area we utilized transition-metal catalysis in order to prepare and evaluate the unconstrained aziridine enamines.

In the area of constrained systems, our studies took advantage of the oxidative stability of unprotected aziridines (Scheme 1). In a preliminary communication, we described the oxidative cycloamination of olefins with *trans*-aziridines through a two-step addition−elimination protocol initiated by *N*-bromosuccinimide. The azabicyclic compounds were synthesized and subsequently converted into substituted pyrrolidine derivatives.[10] In the present paper, we describe substantial expansion of this method to a broad range of substrates including piperidine precursors, control of relative stereochemistry by using *cis*-aziridines, and the possibility of cyclization through intramolecular aziridine addition to aldehydes produced without protecting group manipulations at nitrogen. The scope of aziridine ring-opening reactions is explored through the synthesis of substituted piperidines and pyrrolidines.

## Results and Discussion

At the outset, we considered the aziridine-containing building blocks in which the NH aziridine unit is separated from the olefin by several methylene linkers (Figure 1). If successful, the cyclization of these molecules would deliver piperidine and pyrrolidine derivatives equipped with an aziridine ring. The pyrrolidine and piperidine rings are incorporated into the structures of a wide range of natural products and pharmaceuticals, which makes them an important class of targets for stereoselective synthesis. For example, diverse alkaloids that contain these rings are widely encountered in ants' venoms and amphibian skin.[11,12] If the relative stereochemistry of the initial cyclization products can be controlled, the cycloamination methodology will be a valuable addition to established methods such as stereoselective [3 + 2] cycloadditions and asymmetric aza Diels−Alder reactions.[13] This methodology would offer additional advantages in terms of making diverse pyrrolidine and piperidine derivatives.

The model molecules were prepared from commercially available starting materials. The aziridine functionality was installed by a 1,4-addition of methyl hydroxylamine to α,β-unsaturated ketones followed by a base-promoted elimination of methanol.[14] In the elimination step, *trans*-aziridine was formed exclusively at room temperature (**1a,b**). Upon heating the reaction mixture, the *cis*-aziridine was isolated in 10% yield

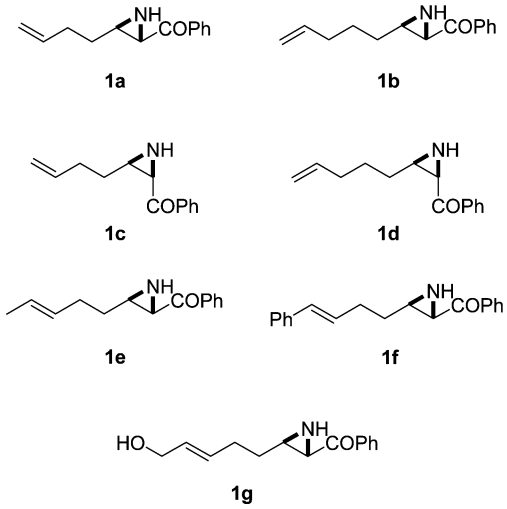



**FIGURE 1.** The aziridine-containing olefins.

(**1c,d**). From the key intermediate **1a**, derivatives **1f** and **1g** were synthesized through functionalization of the terminal olefin by the Heck reaction[15] or by the cross-metathesis.[16] In the case of metathesis, protection of the NH aziridine was found to be mandatory, whereas the Heck coupling took place on the parent NH system using $Pd(OAc)_2/P(o\text{-tolyl})_3$ catalyst. Thereby, the aziridine-containing olefins having structural variations in terms of linker length, substituents on the olefin moiety, and cis/trans isomerism were prepared in a few straightforward steps.

The aziridines **1a**−**g** were converted into the corresponding 1-azabicyclo[3.1.0]hexane or 1-azabicyclo[4.1.0]heptane derivatives **2a**−**g** upon treatment with *N*-bromosuccinimide (Table 1). The reactions were carried out in DME/water[17] or in dichloromethane at different temperatures depending on substrates. The TLC analysis indicated complete conversion of the NH aziridine to the corresponding N−Br species **2k** (Figure 2) within the first 2 min of the reaction.[18] The bromoamine subsequently attacked the double bond of the molecule to give the cycloamination product. The DME/water solvent mixture enabled fast conversion of the starting materials within 2 h. However, when this condition was applied to compounds **1b**−**d**, the bromonium intermediate was preferentially attacked by the solvent water molecule. Instead of the cyclized product, the bromohydrins **2j** (Figure 2) were isolated. After screening a series of solvents, the reaction was found to proceed without the bromohydrin formation in dichloromethane. The new condition B afforded higher yields of the bicycles. For the substrates with *trans*-aziridine and two methylene linkers, the

(9) For an account of recent contributions from our laboratory, see: Watson, D. G.; Yu, L.; Yudin, A. K. *Acc. Chem. Res.* **2006**, *39*, 194−206.

(10) Sasaki, M.; Yudin A. K. *J. Am. Chem. Soc.* **2003**, *125*, 14242−14243.

(11) (a) Dewick, P. M. In *Medicinal Natural Products;* J. Wiley & Sons: Chichester, 1997; Chapter 6. (b) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17* (5), 435−446.

(12) Daly, J. W. *J. Nat. Prod.* **1998**, *61*, 162−185.

(13) For reviews, see: (a) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans.* **2000**, *1* (17), 2862−2892 and references therein. (b) Pichon, M.; Figadere, B. *Tetrahedron: Asymmetry* **1996**, *7* (4), 927−946 and references therein. (c) Higasio, Y.; Shoji, T. *Applied Catal. A: Gen.* **2001**, *221* (1−2), 197−207. For the synthesis of [5.3] bicyclic aziridines, see: (d) Coleman, R. S.; Kong, J.-S.; Richardson, T. E. *J. Am. Chem. Soc.* **1999**, *121*, 9088−9095. (e) Mulzer, J.; Becker, R.; Brunner, E. *J. Am. Chem. Soc.* **1989**, *111*, 7500−7504. (f) Guillemin, J. C.; Denis, J. M. *Angew. Chem.* **1982**, *94*, 715−723. (g) Chaabouni, R.; Laurent, A.; Marquet, B. *Tetrahedron* **1980**, *36*, 877−885.

(14) Sasaki, M, Yudin, A. K. *Synlett* **2004**, *13*, 2443−2444.

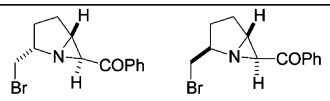
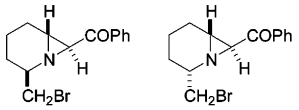
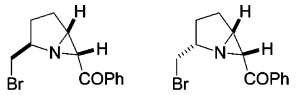
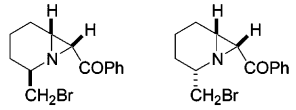
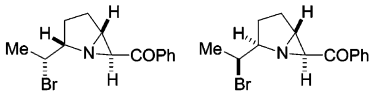
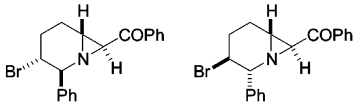
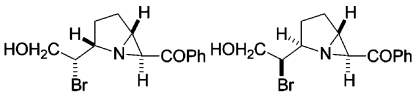
(15) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London, 1985.

(16) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34* (1), 18−29.

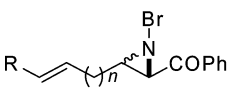
(17) Tamaru, Y.; Kawamura, S.; Bando, T.; Tanaka, K.; Hojo, M.; Yoshida, Z. *J. Org. Chem.* **1988**, *53*, 5491−5501.

(18) We were able to isolate and characterize the N−Cl containing intermediate from **1a** to **2a**.

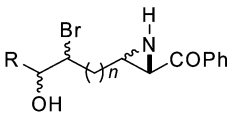
**TABLE 1. Intramolecular Cycloamination of Olefins**

| Entry | Reactant | Condition [a] | Product [b] | Yield |
|---|---|---|---|---|
| 1 | **1a** | B[c] |  **2a** (74:26) | 98 |
| 2 | **1b** | B |  **2b** (78:22) | 88 |
| 3 | **1c** | B[d] |  **2c** ( > 99:1) | 68 |
| 4 | **1d** | B |  **2d** (N / A) | < 5 [e] |
| 5 | **1e** | A |  **2e** (67:33) | 51 |
| 6 | **1f** | A |  **2f** (81:19) | 67 |
| 7 | **1g** | A |  **2g** (67:33) | 51 |

[a] Condition A: DME/water = 4:1, NBS (1.2 eq), 0 °C, 2 h. Condition B: dichloromethane (anhydrous), NBS (1.1 equiv), rt, 30 min, then 40 °C, 24 h. [b] The diastereomeric ratios indicated in brackets were determined by NMR analysis (NOE, HMBC, and COSY). [c] The reaction was carried out at room temperature and was completed in 4 h. Condition A affords a combined yield of 76% with dr of 41:59. [d] The reaction was carried out at room temperature and was completed in 18 h. [e] Starting material was recovered along with a trace amount of product.



**2k**



**2j**

**FIGURE 2.** Bromoaziridine intermediate **2k** and bromohydrin **2j**.

process was faster than for the cis isomers (Table 1, entry 1 and entries 5−7). For the substrates **1b**−**d** containing *cis*-aziridine moieties or three methylene linkers (Table 1, entry 1−4), the cyclization was relatively slow. For example, the aziridine **1a** was converted to bicycle **2a** within 4 h at room temperature (Table 1, entry 1). In the case of **1b**, which contains three methylene linkers, the reaction was much longer and required a higher temperature (Table 1, entry 2).[19] Meanwhile, the *cis*-aziridine **1c** (Table 1, entry 3) was found to react slower than the trans isomer **1a**, but with significantly better diastereoselectivity due to more effective differentiation between the possible transition states in the case of **1c** (TS4 vs TS3 in Figure 3) compared to **1a** (TS2 vs TS1 in Figure 3). In the case of **1d**, a *cis*-aziridine containing three methylene linkers, the initial N−Br intermediate was formed without any difficulty; however, only a trace amount of desired product was found by crude LC/MS (Table 1, entry 4). The aziridines with an aryl-substituted double bond (Table 1, entry 6) preferentially gave the six-membered ring products with bromine addition at the more substituted position. This change of regioselectivity is due to positive charge

(19) Johnson, C. D. *Acc. Chem. Res.* **1993**, *26*, 476−482.

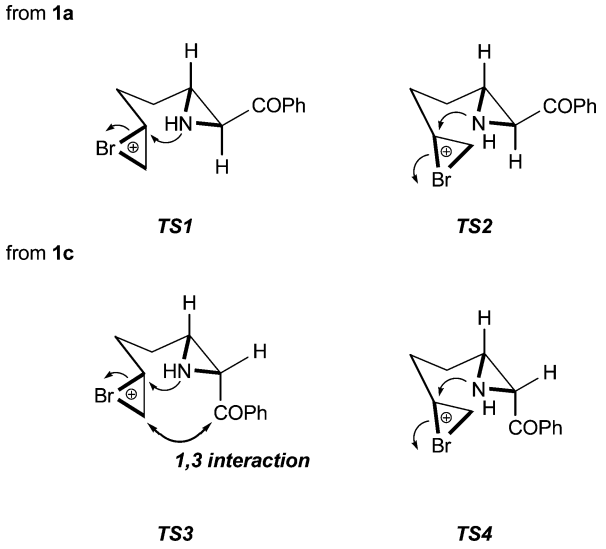
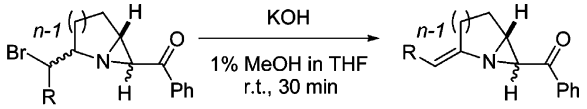
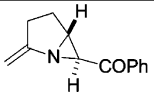
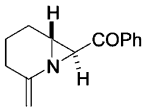
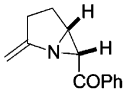
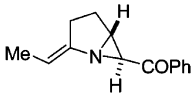



**FIGURE 3.** Proposed transition states leading to **2a** and **2c**.

**TABLE 2. Elimination of HBr to the Strained Bicyclic Enamines**



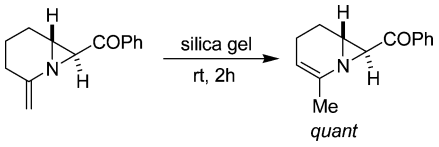

**2a-c and 2e** n = 2 or 3 **3a-c and 3e**

| Entry | Reactant | Product | Yield |
|---|---|---|---|
| 1 | **2a** |  **3a** | 99 |
| 2 | **2b** |  **3b** | 95 |
| 3 | **2c** |  **3c** | 85 |
| 4 | **2e** |  **3e** | 99 |

stabilization at the benzylic position, which affords a polarized bromonium intermediate.

From the diastereomeric bicyclic compounds **2**, the desired strained bicyclic enamines **3** were readily obtained in good to excellent yields by simple dehydrobromination with potassium hydroxide. The reactions proceeded smoothly at room temperature in THF/methanol solution (Table 2). The products were purified by column chromatography and were found to be

**SCHEME 2**




**3b** **3d**

surprisingly stable. A single crystal of **3a** was obtained. The X-ray data shows that the bond length between C(6A) and C(7A) is 1.32 Å, typical of an olefin system. The perpendicular orientation of the nitrogen electron pair in relation to the double bond is evident from crystallographic analysis.[10] This interesting and uncommon structural motif is present in the azinomycin family of antitumor agents.[20] The stereoelectronic effect of aziridine nitrogen causes the enamine to be less nucleophilic and, therefore, more stable in handling compared to similar systems derived from conventional secondary amines. The compound **3b** is not as stable as **3a** and rearranges to the more thermodynamically stable endocyclic enamine **3d** on silica gel (Scheme 2). The aziridine ring in **3** is highly active toward nucleophilic ring opening, which releases the strain of the azabicyclic ring.

The molecules **1a** and **1b** can be further converted into aldehydes **1h** and **1i** by selective oxidation of the terminal olefin. This direct two-step oxidative cleavage gave the aldehyde in quantitative yield (Scheme 3). This chemistry owes its efficiency to the oxidative stability of the aziridine nitrogen, which contrasts with the relative susceptibility of other secondary amines to oxidative conditions that typically necessitates protecting steps. The products underwent intramolecular cyclization in situ to afford diastereomeric hemiaminals **1h** and **1i**. The *N*-acetylaziridinyl aldehydes **1k** and **1l** were obtained by treating the products with acetic anhydride.[21]

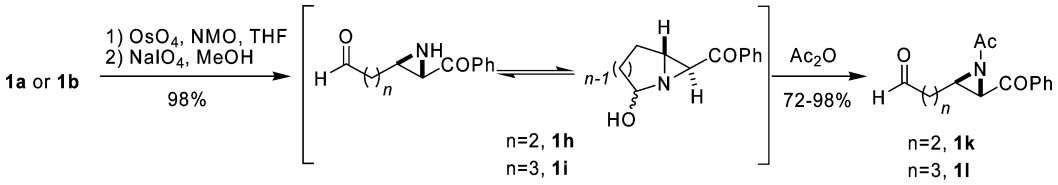
The compound **1h** was obtained as a mixture of two diasteromers, whereas its homologue **1i** contained only 5% of the cyclized product based on $^1$H NMR. When **1h** was treated with trimethylsilyl chloride in the presence of triethylamine, the azabicyclic hemiaminal **2h** was isolated with good diastereoselectivity (Scheme 4). It is instructive to note that the cyclization can be readily controlled by the use of base (cf. formation of **1k** and **1l**). No products arising from iminium ion **1j** were observed due to the high energy barrier required to form the thermodynamically disfavored aziridinium ion (Scheme 4). Therefore, further elaboration at the hemiaminal position on the molecule was not pursued.

The conversion of **1h** into the endo-cyclic enamine **3f** under basic condition was found to be problematic, due to the substantial increase in strain in the target enamine. Additionally, several attempts to direct the aziridine ring opening of **1h**, **1i**, or **2h** under acidic conditions were not successful. The competing reaction at the hemiaminal functionality gave back the linear aziridine-containing aldehydes, which underwent polymerization. The desired cyclic imine products are extremely labile and tend to decompose during the purification process. In an unanticipated development, the aziridine ring was cleanly transformed into cyclic imine under basic hydrazinolysis conditions. Thus, compound **1h** serves as a precursor to pyrrolidine derivatives (Table 3, entry 15).

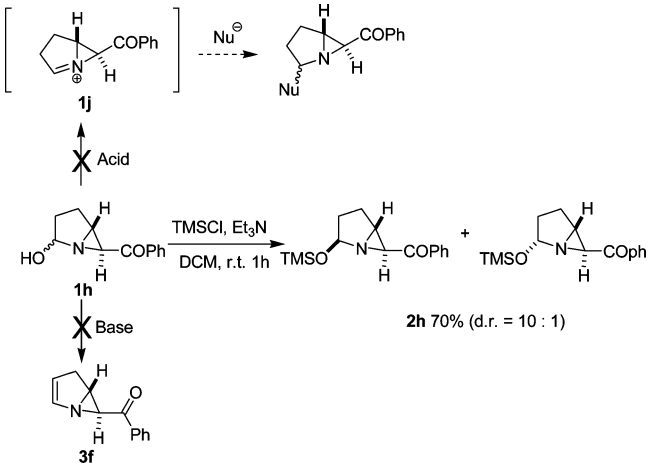
(19) Nagaoka, K.; Matsumoto, M.; Ono, J.; Yokoi, K.; Ishizeki, S.; Nakashima, T. *J. Antibiot.* **1986**, *39*, 1527−1529.

(20) The NMR analysis was complicated due to fast equilibrium between the hemiaminal diastereomers.

**SCHEME 3**



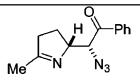
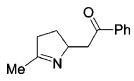
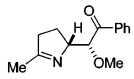
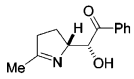
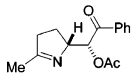
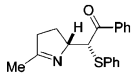
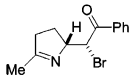
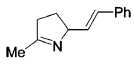
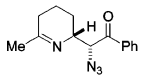
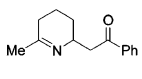
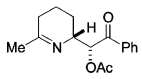
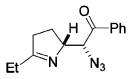
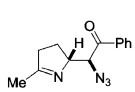
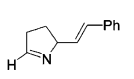
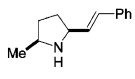

**SCHEME 4**




The ring-opening reactions of **3a**−**e** were found to proceed well with different nucleophiles and to afford high yields and excellent diastereoselectivities in most cases. The reactions are regioselective and preferentially give the corresponding pyrrolidine or piperidine precursors by the ring opening at the α-position (Table 3). The resulting enamines are in situ tautomerized into cyclic imines. When **3a**−**c** and **3e** were treated with trimethylsilyl azide (Table 3, entries 1, 9, 12, and 13), pyrrolidine- or piperidine-derived azides were obtained. We were gratified to observe *stereospecific* transformation of the diastereomers **3a** and **3c** into the corresponding syn or anti products. The aziridine **3a** gave quantitative yield of the syn product with no epimerization, whereas **3c** afforded the anti product along with a trace amount of the epimer, which was separated by column chromatography. The control of the relative stereochemistry of the azido substituent by using *cis*- or *trans*-aziridine precursor has potential application in the synthesis of the core structure of ficellomycin.[22]

Furthermore, reductive ring opening of aziridine **3a** and **3b** by hydrogen on Pd/C gives pyrrolidine or piperidine derivatives in excellent yields (Table 3, entries 2 and 10). Carboxylic acid, alcohol, and water can serve as sources of oxygen nucleophiles to afford the corresponding ester-, ether-, or alcohol-derived pyrrolidine or piperidine derivatives in good yields (Table 3, entries 3, 4, 5, and 11). All of the reactions were carried out under acidic conditions. The aziridine ring opening was also triggered upon basic hydrazinolysis (Table 3, entries 8, 14, and 15).[23] Thus, upon treatment with hydrazine, cyclic allylamines were prepared in moderate to good yields. If the product is further reduced with DIBAL-H, the *cis*-pyrrolidine is obtained in good yields (Table 3, entry 15). The bicycles can also react with sulfur and halogen nucleophiles to afford sulfides and halo derivatives, though in these instances epimerization of the α-stereocenter afforded the mixture of diastereomers.

**TABLE 3. Ring-Opening Reactions of Bicyclic Aziridines**

| Entry | Reactant | Condition | Product | Yield |
|---|---|---|---|---|
| 1 | **3a** | $TMSN_3$ / $H_2O$, DCM |  | 99 |
| 2 | **3a** | Pd / C, $H_2$, MeOH |  | 99 |
| 3 | **3a** | MeOH / $HBF_4$ |  | 65 |
| 4 | **3a** | TFA / $H_2O$ |  | 94 |
| 5 | **3a** | AcOH / DCM |  | 73 |
| 6 | **3a** | PhSH , $HBF_4$ / DCM |  | 36 [a] |
| 7 | **3a** | TMSBr, *n*-$Bu_4NF$ / DCM |  | 63 [b] |
| 8 | **3a** | $H_2NNH_2$, KOH / *t*-BuOH |  | 65 |
| 9 | **3b** | $TMSN_3$ / $H_2O$, DCM |  | 81 |
| 10 | **3b** | Pd / C, $H_2$, MeOH |  | 82 |
| 11 | **3d** | AcOH / DCM |  | 94 |
| 12 | **3e** | $TMSN_3$ / $H_2O$, DCM |  | 95 |
| 13 | **3c** | $TMSN_3$ / $H_2O$, DCM |  | 69 |
| 14 | **1h** | $H_2NNH_2$, KOH / *t*-BuOH |  | 40 |
| 15 | **3a** | 1) $H_2NNH_2$, KOH / *t*-BuOH; 2) DIBAL-H, toluene |  | 63 |

[a] The product epimerizes to afford a mixture of two diastereomers (dr = 70:30 by $^1$H NMR). [b] The product epimerizes to afford a mixture of two diastereomers (dr = 75:25 by $^1$H NMR).

In summary, we have shown that the versatile chemistry of strained bicyclic enamines enables straightforward construction

(21) (a) Argoudelis, A. D.; Reusser, F.; Whaley, H. A. *J. Antibiot.* **1976**, *29* (10), 1001−1006. (b) Kuo, M.-S.; Yurek D. A.; Mizsak, S. A. *J. Antibiot.* **1989**, *42* (3), 357−360.

of a variety of heterocyclic products with high levels of stereocontrol. The unprotected aziridines undergo cyclization through addition−elimination to afford [*n*.1.0] strained azabicyclic enamines or through addition to aldehyde to afford the [*n*.1.0] hemiaminal compounds. In the presence of nucleophiles, the strained bicyclic enamines undergo regio- and diastereoselective ring openings. The strain−release step affords various cyclic imines that are not readily available using conventional protocols. The stereospecificity of these transformations is noteworthy. If the imine functionalities are further reduced in the subsequent step, substituted piperidine or pyrrolidine derivatives can be synthesized. Applications of this methodology in target-oriented synthesis are in progress.

## Experimental Section

**General Procedure for Intramolecular Cycloamination. Method A.** To a mixture of **1a** (2.5 g, 12.4 mmol), dimethoxyethane (100 mL), and water (25 mL) was added *N*-bromosuccinimide (2.65 g, 14.9 mmol) at 0 °C. The mixture was stirred for 2 h in an ice bath. After completion (as judged by TLC), 10% aqueous $Na_2SO_3$ (50 mL) and diethyl ether (100 mL) were added. The layers were separated, and the water layer was extracted with diethyl ether (50 mL). The combined organic layers were dried over sodium sulfate, and the solvent was removed in vacuo. It is essential to maintain the bath at lower than room temperature during solvent evaporation. The residue was purified on a silica gel column (hexane/ethyl acetate = 6/4) to afford (2*R**,5*R**,6*S**)-(2-bromomethyl-1-azabicyclo[3.1.0]hex-6-yl)phenylmethanone (1.08 g) and (2*S**,5*R**,6*S**)-(2-bromomethyl-1-azabicyclo[3.1.0]hex-6-yl)phenylmethanone (1.56 g) (**2a**, combined yield 76%; diastereomeric ratio 41:59). **(2*R**,5*R**,6*S**)-2a**: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.00−8.02 (m, 2H), 7.61−7.64 (m, 1H),7.50−7.53 (m, 2H), 3.68−3.73 (m, 2H), 3.25−3.30 (m, 1H), 3.03 (d, $J$ = 2.5 Hz, 1H), 2.97 (dd, $J$ = 4.5 Hz, 2.5 Hz, 1H), 2.19−2.35 (m, 2H), 2.01−2.06 (m, 1H), 1.78−1.85 (m, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 195.9, 136.9, 133.3, 128.7, 128.2, 66.3, 49.9, 41.5, 35.7, 25.2, 24.4. **(2*S**,5*R**,6*S**)-2a:** $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.99−8.02 (m, 2H), 7.57−7.61 (m, 1H), 7.46−7.50 (m, 2H), 3.68−3.75 (m, 2H), 3.48−3.52 (m, 1H), 3.27 (d, $J$ = 2.5 Hz, 1H), 2.93 (dd, $J$ = 4.5 Hz, 2.5 Hz, 1H), 2.35 (dd, $J$ = 14.0, 8.0, 1H), 2.12−2.19 (m, 1H), 1.95−2.01 (m, 1H), 1.37−1.44 (m, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 195.0, 137.0, 133.3, 128.7, 128.2, 65.0, 49.1, 35.9, 33.1, 27.0, 25.1.

**Method B.** To a mixture of **1b** (0.500 g, 2.33 mmol) and dichloromethane (50 mL) was added *N*-bromosuccinimide (0.456 g, 2.56 mmol) at room temperature. The mixture was stirred for 30 min. After starting material was converted to the N−Br species (judged by TLC, $R_f$ = 0.8 in ethyl acetate/hexanes = 2/8) the mixture was heated at 40 °C for 24 h. Toward the end of the reaction, all of the N−Br species was consumed and precipitate was formed. The reaction was filtrated to remove the insoluble material. The filtrate was concentrated and the residue was purified on a silica gel column to afford (2*R**,5*R**,6*S**)-(2-bromomethyl-1-azabicyclo[4.1.0]hept-7-yl)phenylmethanone (470 mg) and (2*S**,5*R**,6*S**)-(2-bromomethyl-1-azabicyclo[4.1.0]hept-7-yl)phenylmethanone (132 mg) (**2b**, combined yield 88%; diastereomeric ratio 78:22). **(2*R**,5*R**,6*S**)-2b**: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.00−8.03 (m, 2H), 7.56−7.61 (m, 1H), 7.48−7.51 (m, 2H), 3.64 (dd, $J$ = 10 Hz, $J$ = 6.4 Hz, 1H), 3.40 (dd, $J$ = 10 Hz, $J$ = 7.6 Hz, 1H), 3.18 (d, $J$ = 3.2 Hz, 1H), 2.83−2.88 (m, 1H), 2.62−2.65 (m, 1H), 1.97−2.12 (m, 3H), 1.72−1.78 (m, 1H), 1.35−1.39 (m, 1H), 1.16−1.22 (m, 1H). NMR ($CDCl_3$, 100 MHz) $\delta$ 196.9, 137.1, 133.4, 128.8, 128.5, 61.8, 47.4, 42.4, 38.4, 26.7, 21.8, 17.6; HR-MS (ESI) *m*/*z* calcd for $C_{14}H_{17}NOBr$ (M + $H^+$) 294.0488, found 294.0495. **(2*S**,5*R**,6*S**)-2b**:$^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.02−8.05 (m, 2H), 7.57−7.59 (m, 1H), 7.47−7.51 (m, 2H), 3.46−3.62 (m, 3H), 3.35 (d, $J$ = 2.4 Hz, 1H), 2.69−2.71 (m, 1H), 2.07−2.15 (m, 1H), 1.66−1.78 (m, 2H), 1.45−1.57 (m, 1H), 1.20−1.30 (m, 1H). NMR ($CDCl_3$, 100 MHz) $\delta$ 196.6, 137.2, 133.8, 128.8, 128.5, 55.8, 41.5, 40.5, 37.2, 23.3, 20.3, 18.9; HR-MS (ESI) *m*/*z* calcd for $C_{14}H_{17}NOBr$ (M + $H^+$) 294.0488, found 294.0498.

**General Procedure for Dehydrobromination.** To a mixture of **2a** (mixture of diastereomers), THF (200 mL), and methanol (2 mL) was added crushed potassium hydroxide (1.4 g, 25 mmol) at room temperature and the mixture stirred for 4 h. Upon completion (as judged by TLC), dichloromethane (500 mL) and water (300 mL) were added, the layers were then separated, and the water layer was extracted with dichloromethane (150 mL). The combined organic layers were washed with water (200 mL) followed by drying over sodium sulfate, and the solvent was removed in vacuo, to give 1.70 g of (5*R**,6*S**)-(2-methylene-1-azabicyclo[3.1.0]hex-6-yl)-phenylmethanone (**3a**, quant. yield). Further purification was achieved on a silica gel column (hexane/ethyl acetate = 6/4). **(5*R**,6*S**)-(2-Methylene-1-azabicyclo[3.1.0]hex-6-yl)phenylmethanone (3a):** $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.02−8.05 (m, 2H), 7.61−7.65 (m, 1H), 7.50−7.54 (m, 2H), 5.31 (d, $J$ = 1.6 Hz, 1H), 4.74 (d, $J$ = 1.6 Hz, 1H), 3.22−3.25 (m, 2H), 2.24−2.60 (m, 4H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 196.2, 158.6, 136.8, 133.3, 128.7, 128.4, 101.9, 50.6, 45.4, 26.2, 25.3; HR-MS (EI) *m*/*z* calcd for $C_{13}H_{13}NO$ 199.0997, found 199.0998.

**General Procedure of Aziridine Opening with Azidotrimethylsilane. (2*S**,2′*S**)-2-Azido-2-(5′-methyl-3′,4′-dihydro-*2H*-pyrrol-2′-yl)-1-phenylethanone (Table 3, entry 1).** To a mixture of **3a** (380 mg, 1.9 mmol), dichloromethane (10 mL), and water (343 mg, 19 mmol) was added azidotrimethylsilane (440 mg, 3.8 mmol) at room temperature and the mixture stirred overnight. Upon completion (as judged by TLC), the solvent and other volatiles were removed in vacuo to give 460 mg of (2*S**,2′*S**)-2-azido-2-(5′-methyl-3′,4′-dihydro-2*H*-pyrrol-2′-yl)-1-phenylethanone (quant. yield): $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.04−8.07 (m, 2H), 7.65−7.71 (m, 1H), 7.53−7.59 (m, 2H), 5.44 (d, $J$ = 3.6 Hz, 1H), 4.63−4.68 (m, 1H), 2.67−2.79 (m, 1H), 2.49−2.61 (m, 1H), 2.13 (d, $J$ = 1.5 Hz, 3H), 1.81−2.02 (m, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 194.8, 178.1, 134.9, 134.0, 129.0, 128.8, 73.8, 67.5, 39.6, 23.2, 19.7; HR-MS (ESI) *m*/*z* calcd for $C_{13}H_{15}N_4O$ (M + $H^+$) 243.1240, found 243.1246.

**General Procedure of Hydrogenation of Aziridine. 2-(5′-Methyl-3′,4′-dihydro-*2H*-pyrrol-2′-yl)-1-phenylethanone. (Table 3, entry 2).** A mixture of **3a** (20 mg, 0.1 mmol), 10% palladium on carbon (2 mg), and methanol (1 mL) was stirred under hydrogen (1 atm) at room temperature for 1 h. The solid was removed by filtration and the solvent was removed from the filtrate in vacuo, to give 20 mg of 2-(5′-methyl-3′,4′-dihydro-2*H*-pyrrol-2′-yl)-1-phenylethanone (quant. yield): $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.99−8.02 (m, 2H), 7.56−7.61 (m, 1H), 7.46−7.51 (m, 2H), 4.53−4.58 (m, 1H), 3.64 (dd, $J$ = 16.8 Hz, 4.5 Hz, 1H), 2.98 (dd, $J$ = 16.8 Hz, 9.0 Hz, 1H), 2.53−2.61 (m, 2H), 2.26−2.37 (m, 1H),2.07 (d, $J$ = 1.5 Hz, 3H), 1.47−1.60 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 198.6, 175.1, 137.1, 133.1, 128.6, 128.2, 68.8, 45.5, 39.1, 29.6, 19.8.

**General Procedure of Aziridine Opening with Water. (2*S**,2′*S**)-2-Hydroxy-2-(5′-methyl-3′,4′-dihydro-*2H*-pyrrol-2′-yl)-1-phenylethanone (Table 3, entry 4).** To the mixture of **3a** (100 mg, 0.5 mmol) in dichloromethane (5 mL) was added trifloroacetice acid (56 $\mu$L, 0.5 mmol). The reaction was stirred at room temperature for 5 min. Sodium bicarbonate aqueous solution (5 mL) was added. The mixture was extracted with dichloromethane and washed with brine. The combine organic layer was dried and concentrated. The residue was purified by silica gel column (EtOAc) to afford (*2S**,*2′S**)-2-hydroxy-2-(5-methyl-3,4-dihydro-2*H*-pyrrol-2-yl)-1-phenylethanone as a yellow oil (102 mg, 94%): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.01 (d, $J$ = 7.2 Hz, 2H), 7.60 (t, $J$ = 7.2 Hz, 1H), 7.48 (t, $J$ = 8.0 Hz, 2H), 5.59 (b, 1H), 4.42 (b, 1H), 3.81 (b, 1H), 2.52−2.62 (m, 1H), 2.31−2.42 (m, 1H), 2.05 (d, $J$ = 1.2

(22) Chen, G.; Sasaki, M.; Yudin, A. K. *Tetrahedron Lett.* **2006**, *47*, 255−259.

Hz, 3H), 1.42−1.70 (m, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$200.4, 176.7, 134.1, 133.6, 128.9, 128.7, 75.3, 75.2, 40.0, 20.9, 19.6; HR-MS (ESI) *m*/*z* calcd for $C_{13}H_{16}NO_2$ ($M + H^+$) 218.1176, found 218.1186.

**General Procedure for Hydrazine Reduction. 5-Methyl-2-styryl-3,4-dihydro-*2H*-pyrrole (Table 3, entry 8).** A mixture of **3a**, (100 mg, 0.5 mmol), hydrazine monohydrate (250 mg, 5.0 mmol), potassium hydroxide (84 mg, 1.5 mmol), and ethylene glycol (2 mL) was stirred at 100 °C for 30 min. Upon completion as judged by TLC, dichloromethane (10 mL) and water (10 mL) were added, and the aqueous layer was extracted with dichloromethane (5 mL). The combined organic layers were washed with water (10 mL) followed by drying over sodium sulfate, and the solvent was removed in vacuo. The residue was purified on a silica gel column (dichloromethane/methanol = 9/1) to give 5-methyl-2-styryl-3,4-dihydro-2*H*-pyrrole (60 mg, 65%): $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.34−7.45 (m, 4H), 7.24−7.30 (m, 1H), 6.59 (d, $J$ = 11.4 Hz, 1H), 5.59 (dd, $J$ = 11.4 Hz, 9.6 Hz, 1H), 4.92−5.01 (m, 1H), 2.46−2.70 (m, 2H), 2.17−2.28 (m, 1H), 2.11 (d, $J$ = 1.8 Hz, 3H), 1.62−1.75 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 175.5, 137.1, 134.4,129.9, 129.0, 128.1, 126.9, 69.9, 39.4, 30.9, 19.9; HR-MS (EI) *m*/*z* calcd for $C_{13}H_{15}N$ 185.1205, found 185.1202.

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**Supporting Information Available:** Experimental procedures and spectra data for **1a**−**l**, **2c**−**h**, **3b**−**e** and products in Table 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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